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Clinical Features of Hypertrophic Cardiomyopathy Caused by Mutation of a "Hot Spot" in the Alpha-Tropomyosin Gene

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Objectives. **We studied the clinical and genetic features of familial hypertrophic cardiomyopathy (FHC) caused by an Asp175Asn mutation in the alpha-tropomyosin gene in affected subjects from three unrelated families.**

Background. **Correlation of genotype and phenotype has provided important information in FHC caused by beta-cardiac myosin and cardiac troponin T mutations. Comparable analyses of hypertrophic cardiomyopathy caused by alpha-tropomyosin mutations have been hampered by the rarity of these genetic defects.**

Methods. **The haplotypes of three kindreds with FHC due to an alpha-tropomyosin gene mutation, Asp175Asn, were analyzed. The cardiac histopathologic findings of this mutation are reported. Distribution of left ventricular hypertrophy in affected members was assessed by two-dimensional echocardiography, and patient survival rates were compared.**

Results. **Genetic studies defined unique haplotypes in the three families, demonstrating that independent mutations caused the disease in each. The Asp175Asn mutation caused cardiac histopathologic findings of myocyte hypertrophy, disarray and replacement fibrosis. The severity and distribution of left ventricular hypertrophy varied considerably in affected members from the three families (mean maximal wall thickness ± SD: 24 ± 4.5 mm in anterior septum of Family DT; 15 ± 2.7 mm in anterior septum and free wall of Family DB; 18 ± 2.1 mm in posterior septum of Family MI), but survival was comparable and favorable.**

Conclusions. **Nucleotide residue 579 in the alpha-tropomyosin gene may have increased susceptibility to mutation. On cardiac histopathologic study, defects in this sarcomere thin filament component are indistinguishable from other genetic etiologies of hypertrophic cardiomyopathy. The Asp175Asn mutation can elicit different morphologic responses, suggesting that the hypertrophic phenotype is modulated not by genetic etiologic factors alone. In contrast, prognosis reflected genotype; near normal life expectancy is found in hypertrophic cardiomyopathy caused by the alpha-tropomyosin mutation Asp175Asn.**

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Familial hypertrophic cardiomyopathy (FHC) can be caused by a mutation in cardiac troponin T (1), cardiac myosin binding protein C (2,3), beta cardiac myosin heavy chain (4,5), alpha-tropomyosin (1) and essential or regulatory light chains (6). Assessment of the phenotype associated with each mutation in these disease genes has clarified the substantial clinical diversity exhibited by patients with this disorder. That is, some beta cardiac myosin heavy chain mutations (i.e., Arg403Gln) and cardiac troponin T mutations are associated with significant premature death (5,7), whereas life expectancy appears normal (5) with other beta cardiac myosin heavy chain mutations (i.e., Val606Met). The morphologic response produced by these mutations may also show some correlation with genotype; in general, cardiac troponin T mutations produce less cardiac hypertrophy (7) than beta cardiac myosin heavy chain mutations (8).

Alpha-tropomyosin is a component of sarcomere thin fila-

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Abbreviations and Acronyms

Ala63Val = alanine (residue 63) converted to valine
Arg92Gln = arginine (residue 92) converted to glutamine
Arg403Gln = arginine (residue 403) converted to glutamine
Arg453Cys = arginine (residue 453) converted to cysteine
Asp175Asn = aspartic acid (residue 175) converted to asparagine
FHC = familial hypertrophic cardiomyopathy
G→A = nucleotide residue guanine converted to adenine
Glu180Gly = glutamic acid (residue 180) converted to glycine
Val606Met = valine (residue 606) converted to methionine

ments, and that is abundantly expressed in cardiac and skeletal muscle. Although more than 50 different gene mutations have been demonstrated to cause FHC, only three of these (Ala63Val, Glu180Gly and Asp175Asn) occur in alpha-tropomyosin (1,9,10). Limited clinical information has emerged regarding the clinical consequences of these mutations. We report a newly ascertained family (DT) with FHC due to the alpha-tropomyosin mutation Asp175Asn. The cardiac histopathologic findings of this mutation were comparable to those observed in patients with FHC mutations in thick filament proteins. Haplotype analysis of family DT and two other families (DB and MI) bearing the alpha-tropomyosin mutation Asp175Asn indicated that in each the gene defect arose independently. We suggest that the recurrent finding of a G→A transition in exon 5 may reflect increased vulnerability to mutagenesis of alpha-tropomyosin residue 579. The morphologic expression and clinical outcomes were compared in affected members of these families. We conclude that although the hypertrophic response elicited by the alpha-tropomyosin mutation Asp175Asn is variable, the FHC caused by this gene defect is associated with a favorable prognosis.

Methods

Clinical studies. All studies were performed in accordance with institutional review committees at the Abbott-Northwestern Hospital in Minneapolis, Ospedali Galliera in Genoa and Brigham and Women's Hospital. Familial hypertrophic cardiomyopathy affection status was ascertained in all family members by history, physical examination, 12-lead electrocardiogram and two-dimensional echocardiogram, performed as described previously (8,10). Affection status was ascertained without knowledge of genotype. The distribution and pattern of left ventricular hypertrophy was assessed by measurement of wall thickness in four segments of the left ventricle (11).

Genetic studies. Linkage analyses were performed in families using genomic DNA extracted from peripheral blood. Polymorphic loci within or flanking known FHC disease genes on chromosome 1 (1), 7 (12), 11 (2), 14 (5) and 15 (1) were amplified using the polymerase chain reaction as described. Logarithm of the odds scores were calculated using the MLINK program, assuming a disease penetrance of 0.95%.

Haplotype analyses were performed using an intragenic short-tandem repeat polymorphism (HTMαCA) within the alpha-tropomyosin gene (1) and nearby flanking polymorphic locus D15S108 (13).

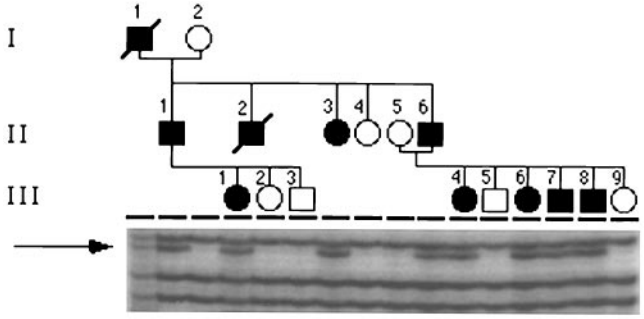


Figure 1. Pedigree of Family DT and detection of the alpha-tropomyosin gene mutation Asp175Asn in affected members. Clinical affection status is shown: **solid symbols** = affected; **open symbols** = unaffected. Deceased individuals are indicated by a **slash**. The dideoxy adenosine triphosphate sequence reactions of a portion of exon 5 is shown below the pedigree. The G→A transition at residue 579 is indicated by the **arrow**. Note that all clinically affected subjects, but none of the clinically unaffected family members, carry the mutation. **Squares** indicate male gender; **circles** indicate female gender; **slashed symbols** indicate deceased individuals.

The Asp175Asn mutation was identified after polymerase chain reaction amplification of exon 5 from genomic DNA extracted from peripheral blood (1) or from a paraffin-embedded tissue sample (14) of ventricular muscle obtained at postmortem examination of one individual. The nucleotide sequence was determined using the Cyclist Taq DNA Sequencing Kit (Stratagene) following the manufacturer's instruction, except that the primer was end-labeled with phosphate-32 gamma-adenosine triphosphate.

Results

Clinical findings. *Family DT.* Ten members of Family DT (Fig. 1) had FHC. Diagnosis was based on clinical studies (Table 1) in eight individuals and at necropsy in two individuals. Individual I-1 died suddenly at age 69 years; individual II-2 died of abdominal hemorrhage and advanced cirrhosis at age 51 years. Autopsy revealed cardiomegaly in each patient (600 g in I-1; 450 g in II-2) and left ventricular hypertrophy. Cardiac histologic examination (Fig. 2, A and B) demonstrated marked myocyte hypertrophy and focal disarray; interstitial fibrosis was prevalent.

Two-dimensional echocardiograms of the eight surviving patients showed left ventricular hypertrophy (left ventricular wall thickness ≥18 mm in each individual; mean [± SD] 24 ± 4.5 mm), which was particularly marked (≥28 mm) in four individuals. The distribution of left ventricular hypertrophy was generally uniform in the family members and predominantly involved the anterior septum (Fig. 3A). Systolic anterior motion of the mitral valve was present in two patients, mild in one and severe (with mitral-septal contact producing marked dynamic outflow obstruction) in the other.

Table 1. Clinical Features of Familial Hypertrophic Cardiomyopathy in 21 Individuals With the Alpha-Tropomyosin Gene Mutation Asp175Asn

				Echocardiography							Electrocardiography		
Patients	Age (yr)/ Gender	NYHA FC	Clinical Profile*	Ant. VS† (mm)	Post. VS† (mm)	ALFW† (mm)	Maximal LVWT	SAM	LVID (mm)	LA (mm)	T Wave Inversion	Inferior or Lateral Qs	LVH
Family DT													
I-1	71/M	?	COPD; unexplained death	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II-1	61/M	II	Syncope; DOE; CAD	28	—	—	28	0	46	46	+	−	−
II-2	51/M	I	Hemorrhage	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
II-3	66/F	I	Syncope	12	22	—	22	0	43	37	+	−	−
II-6	58/M	I	—	18	—	—	18	0	47	54	+	+	−
III-1	38/F	III	DOE; CP; DDD pacemaker	18	18	17	18	Severe: gradient >70 mm Hg	40	39	Pacemaker	−	−
III-4	33/F	II	—	23	23	—	23	0	53	40	+	−	−
III-7	32/M	I	NSVT	28	22	—	28	Mild	48	45	+	−	+
III-6	30/F	I	—	28	18	—	28	0	43	26	+	+	−
III-8	26/M	II	CP; DOE	28	21	—	28	0	42	30	+	−	+
Family DB													
III-2	55/M	I	Syncope	18	—	18	18	Mild	48	40	+	−	−
IV-1	23/M	I	—	14	—	14	14	Mild	48	40	−	+	−
IV-3	17/M	I	—	13	—	13	13	0	39	33	+	+	−
Family MI													
II-4	79/F	II	CP; CAD/AMI; high BP	15	17	17	17	0	48	45	+	−	−
II-7	78/F	II	High BP	—	19	—	19	0	41	40	+	+	+
III-1	55/M	I	High BP	—	20	—	20	0	48	45	+	−	+
III-4	45/M	II	Low BP	20	12	—	20	Mild	43	44	−	−	−
III-6	44/M	I	—	14	—	—	14	—	46	46	−	+	+
III-10	45/F	III	Presyncope; myectomy	12	18	—	18	Mild	44	44	Pacemaker	−	−
IV-2	18/M	I	SCD‡	—	19	—	19	—	50	34	+	−	+
IV-3	21/F	III	Myectomy	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

*Details of patients' clinical profiles are provided in the text. †Wall thickness measurements are provided only for left ventricular segments judged to be hypertrophied. ‡Etiology unclear; sudden cardiac death occurred concurrent with trauma. ALFW = anterolateral free wall; AMI = acute myocardial infarction; Ant. = anterior; BP = blood pressure; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CP = chest pain; DOE = dyspnea on exertion; F = female; FC = functional class; LA = left atrium; LVH = left ventricular hypertrophy; LVID = left ventricular internal diastolic dimension; LVWT = left ventricular wall thickness; M = male; NA = not applicable; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; Post. = posterior; Qs = Q waves; SAM = systolic anterior motion of mitral valve; SCD = sudden cardiac death; VS = ventricular septum.

Family DB. Three members of Family DB were affected (Table 1) and surviving. No FHC-related deaths had occurred in this family. Individual III-2 had one syncopal episode and an episode of nonsustained ventricular tachycardia associated with presyncope. He was treated with amiodarone and has remained asymptomatic for longer than 5 years. His two sons are also asymptomatic.

Left ventricular hypertrophy was mild in Family DB (maximal left ventricular wall thickness ≤18 mm; mean [± SD] 15 ± 2.7 mm) and predominantly involved the anterior septum and contiguous portions of the lateral free wall (Fig. 3B). Mild systolic anterior motion of the mitral valve was present in patients III-2 and IV-2, but was insufficient to produce left ventricular outflow obstruction.

Family MI. Six of eight affected members of Family MI were asymptomatic or mildly symptomatic. Two individuals had severe symptoms: individual IV-3 underwent a myotomy-myectomy operation at age 12 years and currently has only mild symptoms; individual IV-2 was successfully resuscitated from cardiac arrest, which occurred concurrently with a fall at age 18 years—he remains asymptomatic.

Two-dimensional echocardiograms were available in seven affected members of Family MI. The maximal left ventricular wall thickness ranged from 14 to 20 mm (mean [± SD] 18 ± 2.1) and predominantly involved the posterior septum in four patients. Systolic anterior motion of the mitral valve was present in three family members, mild in two and severe in one (IV-3).

The composite disease phenotype exhibited by all affected individuals from these three families included a spectrum of clinical findings but general clinical stability. Eighteen (85%) of the 21 affected individuals had mild or absent symptoms.

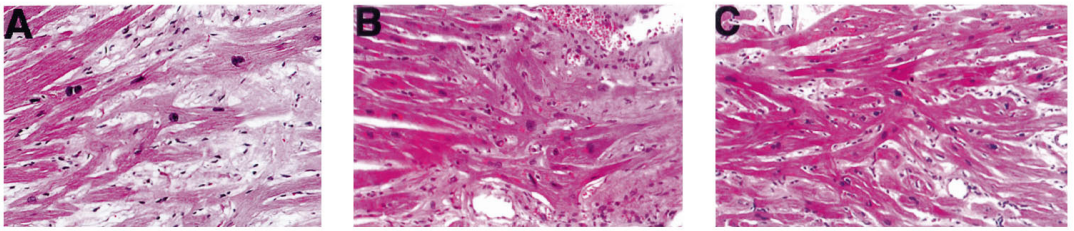
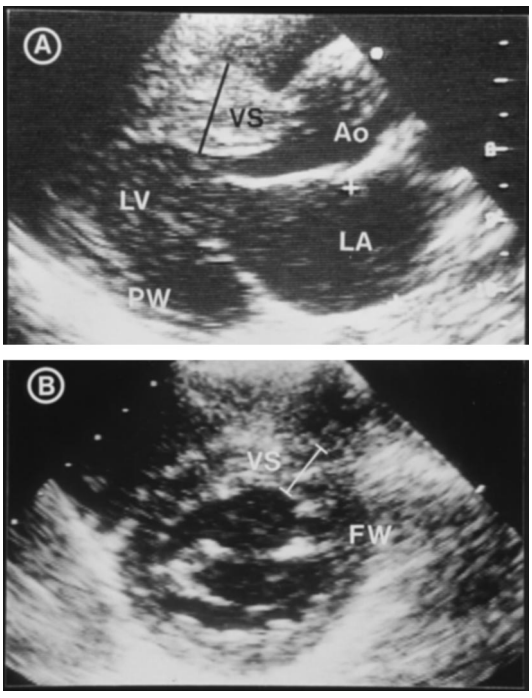


Figure 2. A comparison of the cardiac histopathologic findings observed with the alpha-tropomyosin gene mutation Asp175Asn and the beta cardiac myosin heavy chain gene mutation Arg719Trp. Hematoxylin-eosin staining of postmortem myocardial sections from individuals I-1 (**A**) and II-2 (**B**) of Family DT and of the explanted heart from an affected member of Family 101 (**C**) (15) reveals myocyte disarray, myocyte hypertrophy and interstitial fibrosis. (Magnification × 100, reduced by 35%.)

Electrocardiograms frequently showed deep inferolateral Q waves, anterolateral T wave inversions and left ventricular hypertrophy. Two-dimensional echocardiograms demonstrated nonobstructive FHC in most individuals; a rest outflow tract obstruction was present in <15% of individuals. Longitudinal studies, available in only a subset of affected family members, demonstrated no evolution of cardiac hypertrophy into cardiac dilation.

Figure 3. Echocardiographic images showing diverse morphologic expression of hypertrophic cardiomyopathy caused by the alpha-tropomyosin mutation Asp175Asn. **A,** Individual III-6 (Family DT) exhibits marked hypertrophy (i.e., 28 mm) of the distal anterior ventricular septum (VS). Ao = aorta; LA = left atrium; LV = left ventricle; PW = posterior free wall. **B,** Individual IV-3 (Family DB) has mild left ventricular hypertrophy (i.e., 13 mm) involving the anterior ventricular septum (VS) and a contiguous portion of the anterior free wall (FW). (Calibration dots in **A** and large markings in **B** are 10 mm apart.)



Genetic studies. Linkage analyses in Family DT excluded the FHC genes on chromosomes 1, 7, 11 and 14 (data not shown). Analyses with loci D15S108 and HTMα (1) were fully informative and achieved logarithm of odds scores >3.0 (3.08 and 3.10, respectively), suggesting that FHC in this family was caused by an alpha-tropomyosin mutation. Genomic DNA from two affected individuals of Family DT was amplified by PCR using intronic primers (4) flanking exons of the alpha-tropomyosin gene. Polymerase chain reaction products were sequenced (see Methods). A G→A transition was identified in exon 5, which replaces the normal asparagine (residue 175) with an aspartic acid. Exon 5 was then amplified from DNA samples of all family members and sequenced; the G→A mutation was identified in all clinically affected, but not in clinically unaffected, members of Family DT.

The alpha-tropomyosin mutation Asp175Asn had been previously demonstrated to cause FHC in affected members of Families MI (1) and DB (10). A de novo mutation occurred recently in Family DB (10). To determine whether the gene defect in the two other families occurred because of a founder mutation in an unidentified common ancestor, or because the mutation arose independently in each family, the haplotypes that segregated with the mutated allele were compared. The haplotypes identified by polymorphisms HTMαCA and D15S108 (Table 2) were unique in each family, indicating that an independent mutation occurred in each family at alpha-tropomyosin nucleotide residue 579.

Analysis of survival. The life expectancy associated with the Asp175Asn mutation was assessed in the 21 clinically affected members of the three combined families. A conservative approach was used in assessing disease-related deaths: DT family member I-1, who died unexpectedly of an unknown cause, and MI family member IV-2, who was resuscitated from

Table 2. Disease-Gene Haplotypes in Three Families With Familial Hypertrophic Cardiomyopathy Caused by the Alpha-Tropomyosin Gene Mutation Asp175Asn

	Polymorphism	
Family	HTMαCA	D15S108
DT	3	3
DB	2	3
MI	3	1

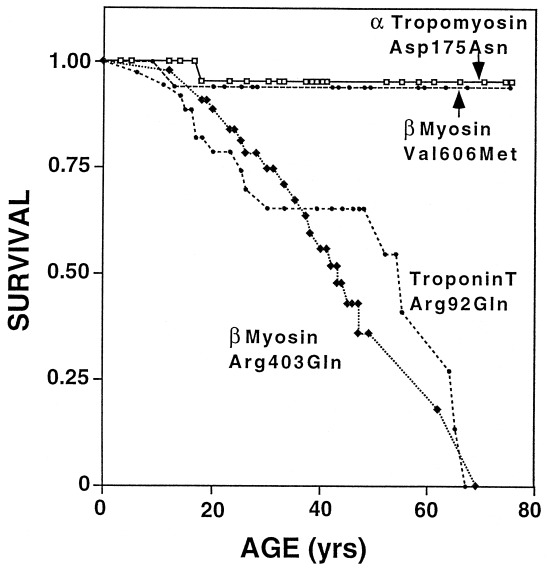


Figure 4. A comparison of Kaplan-Meier product-limit curves for survival in patients with familial hypertrophic cardiomyopathy caused by the alpha-tropomyosin mutation Asp175Asn and other sarcomere gene mutations. Survival of affected individuals was similar in Families DT, DB and MI (data not shown). Survival data were combined and plotted for all 21 affected members of these three families. Survival of patients with familial hypertrophic cardiomyopathy due to the alpha-tropomyosin mutation Asp175Asn was similar to that observed in familial hypertrophic cardiomyopathy due to the beta cardiac myosin heavy chain mutation Val606Met, and significantly better than survival with the beta cardiac myosin heavy chain mutation Arg403Gln or cardiac troponin T Arg92Gln mutation ($p < 0.002$ and $p < 0.003$, respectively).

sudden cardiac death, were scored as deceased. The product-limit survival curve (Fig. 4) substantiated that prognosis in FHC due to the alpha-tropomyosin mutation Asp175Asn was favorable. There were significantly fewer FHC-related deaths from the Asp175Asn mutation than those deaths from FHC caused by the beta cardiac myosin heavy chain mutation Arg403Gln ($p < 0.002$) or the cardiac troponin T mutation Arg92Gln ($p < 0.003$). Survival was comparable to the benign (5,15) beta cardiac myosin heavy chain mutation Val606Met.

Discussion

Although alpha-tropomyosin gene mutations account for <5% of FHC, we have identified three families in which a G→A mutation at nucleotide residue 579 arose independently. Phenotypic analyses of these families have demonstrated that 1) the cardiac histopathologic findings associated with an FHC gene encoding a thin filament component does not differ from that seen with mutated proteins of the sarcomere thick filaments; 2) the hypertrophic response elicited by an FHC gene mutation is dependent on multiple factors; and 3) prognosis is favorable in FHC due to the alpha-tropomyosin gene mutation Asp175Asn.

Independent alpha-tropomyosin Asp175Asn mutations. In addition to the families described in this report, the Asp175Asn mutation has also been reported as a cause of FHC in a family from Japan (9). Although haplotype analyses have not been performed to formally exclude a founding mutation shared by the three families studied herein and the Japanese family, the distinct ethnic backgrounds of all four families makes this unlikely. We suggest that the Asp175Asn mutation has also occurred independently in this fourth family, and we speculate that the high incidence of the Asp175Asn substitution may indicate an increased tendency to mutation of guanine residue 579 in the alpha-tropomyosin gene. This residue is a component of a CpG dinucleotide, which has been previously recognized to have increased susceptibility to mutagenesis within the genome (16). However, because the dinucleotide CpG also occurs elsewhere within the alpha-tropomyosin gene, it is likely that identification of this FHC mutation is enhanced by phenotype selection, because this protein is expressed not only in the heart, but also in all striated muscles (17). Hence, we conclude not only that alpha-tropomyosin residue 579 is a mutational hot spot, but that the normally encoded amino acid residue Asp175 may be of major importance for the function of alpha-tropomyosin in the heart.

Alpha-tropomyosin Asp175Asn and FHC phenotype. In 1960, Hollman et al. (18) reported the cardiac histopathologic findings of FHC. Subsequent genetic studies of this family identified the causal mutation (Arg453Cys) (5) in the beta cardiac myosin heavy chain gene. Because there have been few other examples of FHC cardiac histopathology for which a genetic etiology has been defined, we wondered if the histologic manifestations of FHC varied with genotype. FHC mutations (1) have been identified in components of sarcomere thick filaments (i.e., beta cardiac myosin heavy chain) and components of sarcomere thin filaments (i.e., cardiac troponin T and alpha-tropomyosin). Figure 2 compares the cardiac histopathology of the alpha-tropomyosin mutation Asp175Asn with that found in FHC caused by the beta cardiac myosin heavy chain gene mutation Arg719Trp (15). There is marked similarity in the severity of myocyte hypertrophy, disarray and replacement fibrosis found in FHC caused by defects in sarcomere thin or thick filament proteins. We conclude that common cardiac histopathologic findings can occur in FHC caused by different genetic etiologies.

Varying penetrance has been previously reported for FHC due to different gene defects, with a high penetrance (~95%) for beta cardiac myosin heavy chain mutations and a lower penetrance (75%) for cardiac troponin T gene defects (5,7,19). In the three families described in this report, all adults fulfilled echocardiographic diagnostic criteria for FHC, which implies that the alpha-tropomyosin mutation Asp175Asn is fully penetrant in adulthood.

Although all affected adults had cardiac hypertrophy, left ventricular morphology differed substantially among affected individuals from three pedigrees with an identical alpha-tropomyosin mutation. Marked hypertrophy was demonstrated in Family DT, moderate hypertrophy in Family MI and mild hypertrophy in Family DB (Table 1 and Figure 3). Differences in the magnitude of the hypertrophic response was accompa-

nied by differences in distribution: hypertrophy predominantly involved the anterior ventricular septum (Family DT) or the posterior portion of the septum (Family MI) or the anterior septum and contiguous free wall (Family DB). We conclude that interactions between the alpha-tropomyosin mutation and other genes and environment can substantially influence the morphologic expression of the disease.

Despite the phenotypic differences observed in these three families, the survival of affected individuals was similar. The product-limit survival curve showed a favorable prognosis (Fig. 4) with survival significantly longer than that previously reported for "malignant" beta cardiac myosin heavy chain mutations (5) or cardiac troponin T mutations (7). Life expectancy with the alpha-tropomyosin gene mutation Asp175Asn was similar to that associated with beta cardiac myosin heavy chain mutations regarded as benign (5,15).

Many issues regarding the genetics of FHC and the correlation between genetic alterations and clinical expression of the disease (19,20) remain unresolved. Comparison of the phenotype exhibited by unrelated, affected individuals with an identical FHC mutation provides a unique opportunity to discriminate between clinical findings caused by a particular genetic defect and findings that are influenced by background genes, the environment, or both. Determination of the entire spectrum of genetic and nongenetic factors that influence FHC should improve appropriate risk stratification and management of affected individuals.

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